Int. J. Oral Maxillofac. Surg. 2019; 48: 157–162
https://doi.org/10.1016/j.ijom.2018.07.019, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Head and Neck Oncology

Risk factors and prognosis for the primary intraosseous carcinoma of the jaw

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K. Li, L. Yang, Y.-J. Qiao, Y.-J. Liang, X. Wang, G.-Q. Liao: Risk factors and prognosis for the primary intraosseous carcinoma of the jaw. Int. J. Oral Maxillofac. Surg. 2019; 48: 157–162.

Abstract. Primary intraosseous carcinoma (PIOC) is a rare but aggressive type of odontogenic tumour arising within the jawbone. Diagnosis criteria and treatment strategy remain difficult and controversial. The present study aimed to clarify the clinicopathological features and determine prognostic factors in management of PIOC. A retrospective study of 30 patients with PIOC, treated at the Hospital of Stomatology of Sun Yat-sen University between 2009 and 2017, was conducted. Clinical, histopathological and treatment modality data were collected. Follow-up data were recorded to determine prognostic factors. There were 19 males and 11 females with a mean age of 52.3 years. The most common location of the tumour was the mandible (90%). Having a history of tooth extraction or tooth mobility was the major characteristic symptom (63.3%), jaw swelling coming in second (53.3%). Half of the patients underwent surgery alone. The estimated 2-year overall survival rate (OS) and recurrence-free survival rate (RFS) were 61.3% and 40.1%, respectively. Higher histological grade was an independent risk factor for poor OS (hazard ratio (HR) 0.233 [0.059–0.915], $P = 0.037$), while at pN_+ stage for RFS, HR = 5.627 [1.199–26.409], $P = 0.029$. Because of its rarity and intrabony site, the classification, staging and treatment guidelines for PIOC should be further studied and established.

Key words: primary intraosseous carcinoma; clinicopathological feature; prognosis; overall survival rate; recurrence-free survival rate.

Accepted for publication
Available online 18 September 2018

Primary intraosseous carcinoma (PIOC) is a rare type of histologically proven squamous cell carcinoma arising within the jawbone that cannot be categorized as any other type of carcinoma. It is thought to develop from residues of the odontogenic epithelium or odontogenic cyst or tumour, with no original connection with the oral cavity, which is different from the mucosal oral squamous cell carcinoma[1]. It was first described by Loos in 1913[2], renamed by Willis in 1948[3] as intraalveolar epidermoid carcinoma, and modified to primary intraalveolar epidermoid carcinoma by Shear later in 1969[4]. Previously, the World Health Organization (WHO) recommended the term 'intraosseous carcinoma' in 1971[5], which included both epithelial and mucoepidermoid originated carcinomas. Not until the WHO classification in 2005[1] did 'primary intraosseous squamous cell carcinoma' (PIOSCC) replace the old term and three subcategories were indicated: solid types, squamous cell

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0901-5027/020157 + 06

carcinoma derived from keratocystic odontogenic tumours and those derived from other benign epithelial odontogenic cysts or tumours. In the fourth edition of the WHO *Classification of Head and Neck Tumours* in 2017, the classification was simplified into one type: primary intraosseous carcinoma[6].

Because of its rarity, a comprehensive understanding and a definite diagnosis and treatment plan for PIOC are difficult to obtain[7–9]. Most of the previous studies dealt with only single cases or small series. When compared with the mucosal squamous cell carcinoma (SCC), though the carcinogenic process might be similar, PIOC exhibits different sets of oncogenes and tumour markers, which might indicate different genetic pathways and biologic behavior[10]. The overall prognosis for PIOC is reportedly poor with higher recurrence rates and metastasis rates[11–14]; this might due to the vague symptoms and aggressive behavior of the tumour[15,16]. Furthermore, the WHO 2017 report and the National Comprehensive Cancer Network (NCCN) clinical practice guidelines[17] have not defined the tumour classification of PIOC in detail or the standard treatment for this, leading to controversy. In the present study, we investigated 30 Chinese patients with PIOC to clarify certain novel insights and to identify the risk factors, management and prognosis.

Methods

Materials

We retrospectively reviewed all of the records of the patients with PIOC who were treated at the Department of Oral and Maxillofacial Surgery, Guanghua Hospital of Stomatology, Sun Yat-sen University, from January 2009 to June 2017. The study was approved by the institutional review board of authors' hospital. Demographic data, clinical characteristics, pathological outcomes, treatment modality and follow-up information were recorded. These included sex, age at diagnosis, presenting symptoms (numbness, jaw swelling), preoperative alkaline phosphatase in blood (ALP), radiography, destruction of the bone cortex, resection of the jaw, hospitalization time, postoperative complications, TNM classification, histological grade, use of adjuvant radiotherapy or chemotherapy, recurrence and metastasis. Diagnosis and TNM classification were reclassified by two experienced doctors according to the fourth edition of the WHO Classification of Head and Neck Tumours and the eighth edition of the American Joint Committee classification for oral cavity[18]. All of the patients were subjected to preoperative chest X-rays and magnetic resonance imaging (MRI)/computed tomography (CT) of the head and neck to exclude other primaries. Radiological analyses were carried out by two experienced radiologists to focus on the imaging characteristics and the destruction of cortex. Histological diagnosis of squamous cell carcinoma and grading of tumour and nodal status were defined by two pathologists. Regular follow-up was conducted every 6 months until recurrence or death.

Statistical analysis

Estimated overall survival rates (OSs), recurrent-free survival rates (RFSs) and curves describing survival were generated using the Kaplan–Meier method. Statistical significance was determined by log-rank test. Potential prognostic factors were identified by univariate analysis by the log-rank test. Multivariate hazard ratios (HRs) were analysed using a Cox regression model to identify the independent prognostic factor. On multivariate regression analysis, the backwards method was used. Correlation between clinicopathological factors and endpoints were assessed by the two-tailed Fisher exact test. A P-value of <0.05 was considered statistically significant. Statistical analyses were performed with SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) software application.

Results

Demographic data and clinical characteristics

A total of 30 patients who were diagnosed with PIOC were reviewed. The demographic data and clinical characteristics are presented in Table 1. The patients ranged in age from 24 years to 76 years, with a mean age of 52.3 years. Of the 30 patients, 23 patients (76.7%) were less than 60 years old and 19 patients (63.3%) were male. Twenty-seven tumours (90.0%) were found in the mandible, whereas three cases (10%) were

Table 1. Demography and clinical characteristics of primary intraosseous carcinoma.

Characteristics	No. (%) of patients
Age	
≥60 years	7 (23.3)
<60 years	23 (76.7)
Sex	
Male	19 (63.3)
Female	11 (36.7)
Systemic diseases	
Yes	13 (43.3)
No	17 (56.7)
History of teeth extraction or mobility	
Yes	19 (63.3)
No	11 (36.7)
Smoking	
Yes	9 (30.0)
No	21 (70.0)
Onset time	
≤3 months	13 (43.3)
>3 months	17 (56.7)
Lip or facial numbness	
Yes	10 (33.3)
No	20 (66.7)
Jaw swelling	
Yes	16 (53.3)
No	14 (46.7)
Location of tumour	
Maxilla	3 (10.0)
Mandible	27 (90.0)
Sides of tumour	
Unilateral	26 (86.7)
Bilateral	4 (13.3)
Destruction of bone cortex	
Yes	20 (66.7)
No	10 (33.3)
Preoperative alkaline phosphatase	72.5 ± 21.1 (U/L)

Table 2. Pathologic and treatment characteristics of primary intraosseous carcinoma.

Characteristics	No. (%) of patients
Histologic grade	
Grade 1	22 (73.3)
Grade 2	8 (26.7)
Margin	
Negative	30 (100.0)
Primary tumour surgery	
Marginal maxillectomy or mandibulectomy	1 (3.3)
Segmental resection	9 (30.0)
Hemi-resection of maxilla or mandible	11 (36.7)
Three-quarter or total resection of maxilla or mandible	9 (30.0)
Neck dissection	
Yes	22 (73.3)
No	8 (26.7)
Type of defect	
Mandible ($n = 27$)	
Class I	1 (3.3)
Class Ic	2 (6.7)
Class II	2 (6.7)
Class IIc	12 (40.0)
Class III	4 (13.3)
Class IV	3 (10.0)
Class IVc	3 (10.0)
Maxilla ($n = 3$)	
Class IIb	1 (33.3)
Class IId	1 (33.3)
Class IIIb	1 (33.3)
Simultaneous reconstruction	
Yes	27 (90.0)
No	3 (10.0)
Type of reconstruction ($n = 27$)	
Vascularized fibular osteomyocutaneous free flap	20 (74.1)
Pectoralis major myocutaneous flap	3 (11.1)
Others*	4 (14.9)
T stage	
T_{4a}	30 (100.0)
pN stage	
N_X	8 (26.7)
N_0	6 (20.0)
N_1	16 (53.3)
M stage	
M_0	30 (100.0)
Radiotherapy	
Yes	12 (40.0)
No	18 (60.0)
Chemotherapy	
Yes	5 (20.0)
No	25 (80.0)
Treatment	
Surgery alone	15 (50.0)
Surgery + radiotherapy/chemotherapy	13 (43.3)
Surgery + radiotherapy + chemotherapy	2 (6.7)
Postoperative complication	
Yes	8 (26.7)
No	22 (73.3)
Hospitalization time	25.5 ± 10.2 (days)

Grade 1, well-differentiated squamous cell carcinoma; Grade 2, moderately differentiated squamous cell carcinoma; Grade 3, poorly differentiated squamous cell carcinoma.

* Including vascularized iliac crest free flap, vascularized anterolateral thigh flap and frontal muscle flap.

located in the maxilla. All of the mandibular and maxillary tumours involved the posterior region of the jaws. The median onset time was 4.2 months (interval between onset of the initial symptoms and time of visiting our department), ranging from 1.5 months to 36 months. Having a history of tooth extraction or tooth mobility was the major characteristic symptom in 19 patients (63.3%). A total of 16 patients (53.3%) also complained of jaw swelling and 10 patients (33.3%) presented signs of lip or facial numbness. Radiographically, all tumours showed radiolucent lesions, with osteolytic bone changes. Twenty-six tumours (86.7%) occurred in unilateral jaw, while four tumours crossed the midline. Destruction of the bone cortex was found in 20 tumours (66.7%). No statistical relationship was found between bone destruction and clinical symptoms (numbness or swelling) ($P > 0.05$). All patients exhibited normal levels of serum ALP.

Treatments and pathologic characteristics

Pathologic and treatment characteristics of PIOC are presented in Table 2. All of the patients underwent initial treatment involving primary tumour resection with or without the neck dissection at the time; 36.7% of patients underwent hemiresection of the jaw, while 30% underwent segmental resection and 30% underwent three-quarter or total resection of jaw. Intraoperative frozen sections of the soft tissue were carried out. No positive margin was found. Margins of both the soft tissue and hard tissue were histologically proven negative by the paraffin sections. Twenty-two patients (73.3%) underwent a neck dissection if cN_+ was diagnosed preoperatively based on the palpation or radiology. Defects of the mandible and maxilla were surgically classified using Brown's classifications. For the mandibular defect, Class IIc ranked first (12/27, 44.4%), with Class III coming second (4/27, 14.8%). Each of the Class IIb, Class IId and Class IIIb of the maxilla defect had one case. Almost all patients (90%) had simultaneous reconstruction of defect. Vascularized fibular osteomyocutaneous free flap (20/27, 74.1%) was the major choice for the reconstruction, followed by the pectoralis major myocutaneous flap (3/27, 11%). Fifteen patients (50.0%) underwent surgery alone. All of the patients were recommended for the postoperative adjuvant therapies. However, only 10 and three patients received postoperative radiotherapy or chemotherapy, respectively. Only two patients were treated with both of these adjuvant therapies. Twenty-two tumours (73.3%) accounted for histologic grade I (well differentiated), while eight (26.7%) were histologic grade II (moderately differentiated). All patients were categorized as T4a stage. Pathological positive nodal statue was observed in 16 patients (53.3%) which were classified as pN_1 stage, while pN_0 stage accounted for 20.0% of patients. Eight patients remained

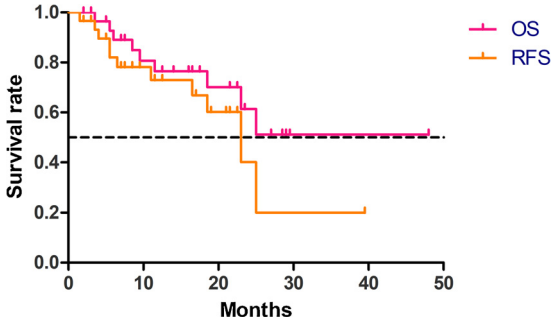

Fig. 1. Kaplan–Meier survival curve of overall survival (OS) and recurrence-free survival (RFS) rates.

Table 3. Univariate survival and recurrence analysis of clinical and pathologic variables of primary intraosseous carcinoma.

Variables	OS		RFS	
	2 y, %	*P*	2 y, %	*P*
Gender				
Male	57.1		31.6	
Female	76.2	0.725	53.0	0.755
Age				
≥60 years	66.7		20.8	
<60 years	47.9	0.419	50.7	0.175
History of teeth extraction or mobility				
Yes	54.3		27.1	
No	48.0	0.689	72.7	0.408
Lip or facial numbness				
Yes	54.7		42.7	
No	63.9	0.496	34.6	0.555
Destruction of bone cortex				
Yes	31.6		49.7	
No	88.9	**0.050***	88.9	0.112
Histologic grade				
Grade 1	74.2		48.9	
Grade 2	29.2	**0.016***	23.4	**0.012***
Neck dissection				
Yes	58.8		39.4	
No	71.40	0.784	58.3	0.824
pN stage				
Non pN_+	85.1		82.0	
pN_+	35.1	**0.029***	18.4	**0.014***
Adjuvant therapy				
Yes	65.7		36.7	
No	61.7	0.459	44.7	0.202

OS, overall survival rate; RFS, recurrence-free survival rate; Grade 1, well-differentiated squamous cell carcinoma; Grade 2, moderately differentiated squamous cell carcinoma.
* Statistically significant result.

at pNx. All of the patients presented no metastasis at the time of diagnosis. Postoperative complications were detected in eight patients (26.7%), including pneumonia, vascular crisis and wound infection.

Outcomes

Follow-up length for the 30 patients ranged from 2 months to 48 months (mean, 16.3 months), during which contact was lost with four patients. At the time of current study, nine patients died of disease. Six patients (20%) developed local recurrence in the primary tumour site, while two (6.7%) had regional recurrence in the neck. One patient developed distant metastasis. Using the Kaplan–Meier analysis, the estimated 1-year OS and 2-year OS were 76.5% and 61.3%, respectively (Fig. 1). On univariate analysis, destruction of bone cortex ($P = 0.050$), histologic grade ($P = 0.016$) and pN stage ($P = 0.029$) were significant prognostic factors for survival (Table 3). On multivariate analysis, however, only histologic grade was a significant independent risk factor of PIOC survival (HR 0.233 [0.059–0.915], $P = 0.037$) (Table 4; Fig. 2). Patients with less well-differentiated tumours were assumed for the poor prognosis. The accumulated probabilities of recurrence, or RFS, at 1 and 2 years were 72.9% and 40.1%, respectively (Fig. 1). Univariate analysis showed that histologic grade ($P = 0.012$) and pN stage ($P = 0.014$) were significant prognostic factor for recurrence (Table 3). On multivariate analysis, only pN stage remained a significant independent risk factor for recurrence (HR 5.627 [1.199–26.409], $P = 0.029$) (Table 4; Fig. 1). Patients with positive nodes in the neck have higher probability to recur. By contrast, no statistically significant difference was observed in OS and RFS between patients with and without the following features: gender, age, history of tooth mobility or extraction, lip or facial numbness, subtypes, neck dissection and adjuvant therapy.

Table 4. Multivariate survival and recurrence analysis of clinical and pathologic variables of primary intraosseous carcinoma.

Variables	OS		RFS	
	P value	HR (95%CI)	*P* value	HR (95% CI)
Histologic grade	0.037*	0.233 (0.059–0.915)	–	–
pN stage	–	–	0.029*	5.627 (1.199–26.409)

CI, confidence interval; HR, hazard ratio; OS, overall survival rate; RFS, recurrence-free survival rate.
*Statistically significant result.

Discussion

PIOC is a rare malignant epithelial tumour that occurs exclusively in the jawbones, with no initial communication with the oral mucosa. Because of its rarity and unclear biological behaviour, further insights and data should be studied and help to develop novel treatments. Therefore, the aim of present study was to analyse the clinicopathologic characteristics and prognosis and to identify the risk factors based on this series of 30 cases.

In general, the overall prognosis for PIOC is poor with low survival rates and high recurrence rates. Previous studies reported that the 2-year survival rate was around 60∼70%, while 5-year survival rate was around 30∼40%[15,16,19]. Our study showed similar estimated results. It is difficult to make a definite diagnosis at the early stage of PIOC and detection delay easily results, based on the vague

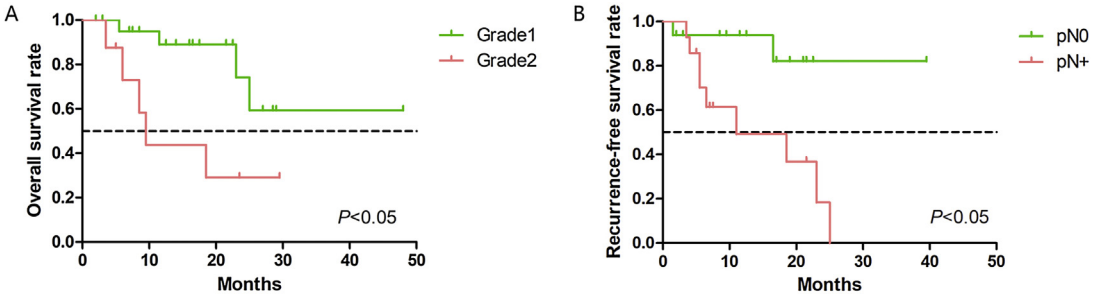

Fig. 2. Overall survival by histological grade (A) and recurrence-free survival by pN stage (B).

symptoms. When patients come into clinic, they usually present with the jaw swelling and paresthesia, indicating the cortex breakthrough and perineural invasion[11,15,20,21]. Also, the possibility of delayed diagnosis might be due to the less frequent dental visits or to a lack of standard radiology examinations before extraction[15,22].

Squamous cell carcinoma growing in the jawbone is different from that in the oral mucosa in many aspects such as tumorigenesis and tumour biology. Using laser capture microdissection and functional genomic comparison, Alevizos et al.[10] found that PIOC possessed different oncogenes and tumour suppressors. Imitating a 'friend' in the bone microenvironment might be a way for tumours to escape immunological surveillance in tumour development. This process is called osteomimicry[23,24]. Because of it, we might also fail to get a clear safe margin during resection even with a negative result of frozen section in the operation[25]. Moreover, the intraoperative bone margin is now recommended to be obtained from the cytological frozen section of the marrow. Forrest et al.[26] and Hinni et al.[27] showed that further techniques such as cytological frozen section and molecular margin can be applied to obtain complete surgical excision; however, these methods are highly technically demanding and sensitive.

Unlike that of the mucosal SCC, histological grading of PIOC strongly impacted on the prognosis. As an independent risk factor in the present study, some previous studies showed similar results that poorly differentiated tumours correlated with aggressive biological behaviour[15,16,28,29]. Based on the 2005 classification with three subtypes, it is reported that most of this type lie in the tumours arising de novo (subtype I). If we reclassified the tumours, all eight that were moderately differentiated tumours in our study were subtype I PIOSCC. Lukandu et al.[22] suggested that subtype I of PIOSCC might be the late stage of the other two types, of which long onset time before consciousness further contributed to the tumour progression.

For highly malignant tumours based on the staging system of American Joint Committee on Cancer (AJCC), multimodality therapy is recommended according to NCCN guidelines. However, for PIOC, nowadays there is no specific staging system or treatment guideline. Though the AJCC classification for oral cancer was used in this study, this staging system was still far from perfect. As an important factor, histological grading is not considered in the prognosis stage group. Also, because the tumour is growing inside the bone, the intrabony site might lead to different growth rates and neighbouring structure destruction. Half of patients in our study underwent surgery alone, while the rest received either or both of the radiotherapy and chemotherapy. Two-year OS showed no significant difference between with and without adjuvant therapy groups. Naruse et al.[19] believed that because of the consistent OS with that of stage IV oral cavity lesion, treatment should be similar to that for oral cavity cancers with at least T3N0. Controversy among different authors makes treatment strategy need for further investigation. Our recommendations on the management of PIOC are radical resection of the jaw, at least hemi-resection, with or without condylar resection. Therapeutic neck dissection was carried out based on the preoperative evaluation. Intraoperative frozen sections of the soft tissue and bone are recommended. Adjuvant therapies are needed and close follow-up should be undertaken.

This study has some limitations including the small sample size and short follow-up period. A large portion of advanced cases were detected in our study with 70% of subtype I. Since PIOC is a diagnosis of exclusion, it requires histological, radiographical and clinical information for comprehensive analysis. Its complexity makes it difficult to identify the origin, which might be also one of the reasons why they simplified the classification in the 2017 edition. The incidence of PIOC is low and the diagnoses in the past may have easily been confused with the SCC of gingiva. Thus, multicentre studies and thorough presurgical evaluations are needed. Few studies carried out a comparative study across the world. For survival analysis as well as clinicopathological observation, enrolling patients and follow-up work will be continued.

In conclusion, as a rare carcinoma, PIOC behaved aggressively with little documented data. The estimated 2-year OS and RFS were 61.3% and 40.1%, respectively. Higher histological grade was an independent risk factor for OS indicating poor prognosis, while pN_+ stage was the independent risk factor for RFS. The management of surgical margin and influence of adjuvant therapy remain uncertain. Further research should be carried out on classification, staging and standard treatment strategy specializing for PIOC.

Funding

There was no funding to declare.

Competing interests

None.

Ethical approval

The present study was approved by the ethics committee of the University and adhered to the tenets of the Declaration of Helsinki.

Patient consent

Not required.

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